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Genetics of homocysteine metabolism and associated disorders

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Abstract

Homocysteine is a sulfur-containing amino acid derived from the metabolism of methionine, an essential amino acid, and is metabolized by one of the two pathways: remethylation or transsulfuration. Abnormalities of this pathway lead to hyperhomocysteinemia. Hyperhomocysteinemia is observed in approximately 5% of the general population and is associated with increased risk for many disorders, including vascular and neurodegenerative diseases, auto immune disorders, birth defects, diabetes, renal disease, osteoporosis, neuropsychiatric disorders and cancer. We review the correlation of homocysteine metabolism and the disorders described above and genetic variants on genes encoding for enzymes of homocysteine metabolism relevant to the clinical practice, especially common variants on *MTHFR* gene.677C>T and 1298A>C.

Keywords

homocysteine; hyperhomocysteinemia; folate metabolism; single nucleotide polymorphism; susceptibility genes

Introduction

Homocysteine (Hcy) is the demethylated derivative of methionine, which is, after conversion to S-adenosylmethionine (SAM), the most important methyl group donor in the body. Homocysteine is a sulfur-containing amino acid derived from the metabolism of methionine, an essential amino acid, and is metabolized by one of the two pathways: remethylation or transsulfuration (Figure 1). In remethylation, homocysteine forms methionine by the addition of a methyl group from 5-methyltetrahydrofolate or betaine. The 5-methyltetrahydrofolate is the result of the conversion of folic acid from the diet to 5-10-methyltetrahydofolate and finally to 5-methyltetrahydrofolate by the enzyme 5,10-methyltetrahydrofolate reductase (MTHFR). In all tissues, the cofactor vitamin B12 participate in the remethylation reaction with 5-methyltetrahydrofolate, whereas the reaction with betaine is restricted to the liver and independent of vitamin B12. The methionine is then activated by ATP to form SAM , a universal methyl donor to a variety of acceptors. In the transsulfuration pathway HCY is converted to cystathionine by cystathionine β-synthase and finally to cysteine using vitamin B6 as a cofactor (1).

Therefore plasma homocysteine levels are determined by several factors, such as the cofactors vitamin B12, vitamin B6 and folic acid and enzymes involved in methionine

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metabolism. Their levels are inversely correlated, with plasma homocysteine levels increasing as vitamin B concentrations decrease (2).

In circulation 80-90% of homocysteine is protein bounded, 10-20% of the total homocysteine (tHcy) is present as homocysteine-cysteine mixed disulfide and homocystine (dimer of homocysteine) and less than 1% remaining is present in the free reduced form (3).

Homocysteine and MTHFR

The MTHFR is an important enzyme in the homocysteine metabolism and catalyzes the conversion of 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, the predominant circulating form of folate. The *MTHFR* gene has at least two functional polymorphisms, 677C>T and 1298A>C. The *MTHFR* 677T allele is associated with reduced enzymatic activity, decreased concentrations of folate in serum, plasma, and red blood cells, and mildly increased plasma total homocysteine (tHcy) concentrations (4;5).

MTHFR polymorphism 1298A>C also affects MTHFR activity but without biochemical changes (6). Normal MTHFR activity is crucial to maintain the pool of circulating folate and methionine and to prevent the accumulation of Hcy (4).

Double heterozygous for *MTHFR* 677C>T and 1298A>C polymorphisms result in a lower MTHFR activity, as compared to heterozygosity for either of the *MTHFR* variants separately (6). Individuals with the 677TT genotype, have approximately 30% the MTHFR enzyme activity of those with the 677CC genotype, whereas heterozygotes 677CT have around 65% of enzymatic activity (7).

Hyperhomocysteinemia

In healthy people, blood levels of hyperhomocysteinemia (HHcy) are age and gender related. Plasma levels of Hcy are higher in men than in women (8) and increase from 10.8mmol/L at age 40–42 up to 12.4mmol/L between 65 and 67 years (9). Hyperhomocysteinemia is classified as moderate (15–30mmol/L), intermediate (31–100mmol/L) or severe (>100mmol/L) (10).

HHcy in humans can also be distinguished by category, including cause, prevalence and severity. The more severe cases are due to homozygous defects in genes encoding for enzymes of homocysteine metabolism (Table 1).

HHcy is observed in approximately 5% of the general population and it has been associated with many disorders. Below we review several disorders that have been related to abnormal homocysteine metabolism.

Hyperhomocysteinemia and Neural tube defects

Neural tube defects (NTD) remain one of the commonest birth defects worldwide. NTD result from failure of neural tube formation or closure during the first 28 days of pregnancy. Studies also supported the use of folic acid in the prevention of the first occurrence of NTD (11). These findings suggest that impaired folic acid metabolism play a role in NTD.

Several studies were reported that high maternal homocysteine levels was associated with a increased risk for offspring with NTD in different populations (12-18). A case-control study conducted in Brazil showed that mothers with NTD children had increased tHcy levels when compared with control mothers. The case mother also had low vitamin B12 compared to control mothers. No differences in the *MTHFR* polymorphisms were identified in mothers, children with NTD or controls (19) Another Brazilian study also was not able to identified

MTHFR polymorphism and NTD, suggesting that this gene does not play a role in NTD in Brazilian population (20).

Hyperhomocysteinemia and Nonsyndromic Oral Clefts

Oral clefts are common birth defects whose prevalence differs between geographical regions and ethnic groups. They have a complex, multifactorial inheritance involving genetic and environmental factors.

A case-control study showed that mother of clefting children had higher plasma tHcy concentrations in fasting as well as after methionine afterload test comparing to control mothers., suggesting that impaired folic acid metabolism play a role in clefting (21). A recent study has indicated periconceptional use of folate could prevent the ocurrence of cleft lip and palate but not of cleft palate only (22).

A study demonstrated a significant increased risk of having a child with CL/P if the mother was heterozygous for both common *MTHFR* polymorphisms (23). The risk of a child with CL/P was only significantly increased if mothers, carrying *MTHFR* 677TT or *MTHFR* 1298CC genotype also had a low periconceptional intake of dietary folate and/or folic acid supplements suggesting that the two *MTHFR* polymorphisms were independent risk factor for CL/P (24).

Hyperhomocysteinemia and Congenital heart defects

Congenital Heart Defects (CHD) occurs among 11 per 1000 live births in the United States. Annually, account for approximately 6000 total deaths and one-tenth of infant deaths in USA. CHD develop during the first three weeks after conception and are common congenital anomalies of multifactorial origin influenced by genetic and environmental factors (25). A meta-analysis demonstrated that maternal HHcy was significantly associated with a increased risk of having a child with a CHD suggesting that maternal HHcy is an important risk factor for CHD (24).

Hyperhomocysteinemia and Cardiovascular disorders

Vascular diseases are commonly associated with traditional risk factors as for example systemic arterial hypertension, diabetes mellitus and smoking, but in the last decade other risk markers have been identified, one of them being homocysteine. Various studies had identified hyperhomocysteinemia as an independent risk factor for coronary artery disease (CAD). The relationship between *MTHFR* polymorphism and the severity of CAD in patients undergoing coronary artery bypass surgery showed that homocysteine levels was significantly higher in patients with CAD than in control subjects and the genotype of *MTHFR* 677C>T was associated with the extent of CAD in patients at high risk for this pathology (26).

A study compared postmortem serum HCY levels of men who died suddenly of severe CAD and controls. Serum Hcy levels were elevated in men who died with coronary thrombus compared to controls. This study also showed that the risk was increased if there was concomitant diabetes mellitus and presence of lipid-poor and plaques. Whether elevated serum Hcy might be causally associated with sudden death or merely a marker of a process related to sudden death is still unclear (27).

Hyperhomocysteinemia and Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the arteries, in which deposits of fatty substances, cholesterol, calcium and other substances build up in endothelial layer of

arteries. Several studies had identified moderate hyperhomocysteinemia as an independent risk factor for atherosclerotic disease (10)

Accelerated atherosclerosis had been demonstrated in apolipoprotein E-deficient (apoE-/-) mice with hyperhomocysteinemia diet and in cystathionine-synthase (CBS)/apoE-/- double-knockout mice (28,29). These findings suggest that HHcy accelerates atherogenesis in hyperlipidemic mouse model that develops spontaneous atherosclerosis. However, a causal relationship between atherogenesis and HHcy had not been established in other species, including rats, rabbits, pigs, and primates (30,31).

Hyperhomocysteinemia and Down Syndrome

Down Syndrome (DS) occurs due to three copies of chromosome 21, in most cases due to the failure of chromosomal segregation during maternal meiosis. The risk of DS is directly correlated to increased maternal age. An important factor that could modulate the maternal risk for DS is plasma HHcy concentration. An elevated risk for DS in the presence of the *MTR* 2756G allele, in combination with elevated HHcy concentration was observed (32). However, the association of this polymorphism with the risk for DS was not confirmed by additional study (33).

A study conducted in Brazil with mothers of children with DS and control mothers analyzed tHcy and several variants in the folate pathway (*MTHFR* 677C>T, *MTHFR* 1298A>C, *MTRR* 66A>G, *MTR* 2756A>G, and *CBS* 844ins68) showed homocysteine levels were higher among DS mothers compared to controls. Only the 677T allele was associated with altered levels of tHcy in the case group. All genotype distributions were similar in the two groups, but the frequency of the 677T allele in the case group was significantly higher. All the other polymorphisms did not show an association with risk for DS, when evaluated separately. However, when the presence of the alleles was evaluated together, the mothers of children with DS tend to have a higher number of variant alleles than the control mothers (34).

The effect of plasma HHcy concentrations on maternal risk for DS showed Hcy concentrations significantly higher in DS mothers as compared to control group. This result showed that Hcy concentrations were significantly different in women with *MTHFR* 1298CC genotype in DS mothers than in control mothers (35).

Hyperhomocysteinemia and Smoking or Pregnancy

Cigarette smoking has been associated with oxidative stress and increased risk of many chronic diseases. Smoking induces depletion of cellular antioxidant and is also known to be associated with an increased homocysteine level. Several studies observed increase of plasma tHcy in smokers than non smokers subjects (36,37).

During pregnancy there is an increase of Hcy levels for each trimester of pregnancy and decrease of folate levels. Additionally, folate levels continue to decrease after pregnancy (38). Maternal smoking also alters total homocysteine concentration in infants. The serum homocysteine concentrations were significantly higher in smoking as compared with nonsmoking pregnant women as well as in umbilical cord blood of their newborns (39).

Hyperhomocysteinemia and Alzheimer's disease and Vascular dementia

Low folate and raised Hcy concentrations in blood are associated with poor cognitive performance in the general population. Elevated levels of Hcy result in neurotoxic and vasotoxic effects in dementia and Alzheimer's disease suggesting that Hcy is a direct marker for early cognitive decline (40). However, the pathogenesis of HHcy is still not clear in

vascular dementia. The levels of serum folate, vitamin B12 and plasma Hcy were studied in vascular dementia and Alzheimer, and the authors found that Hcy was increased, while folate and vitamin B12 decreased in both of these diseases. This suggests that supplementation of folic acid and vitamin B12 could be benefit in Alzheimer's disease and dementia (41)

A randomized, double blind, placebo controlled study was conducted in Netherlands. There were included 818 subjects, men and post-menopausal women aged 50-70 years who used placebo or 800μg/day folic acid for 3 years. Serum folate concentrations increased and plasma Hcy concentrations decreased in participants taking folic acid compared with those taking placebo. This study also showed that supplementation of folic acid improved significantly the decline of cognitive function related to age (42).

Hyperhomocysteinemia and Breast cancer

High intake of folate, which is plentiful in vegetables and fruits, has been associated with reduced risk of several cancers. Folate deficiency was suggested to increase the risk of cancer through impaired DNA repair synthesis and disruption of DNA methylation that may lead to protooncogene activation (43). It is biologically plausible that polymorphisms or gene–environment interactions rather than the folate intake alone would have the impact on breast cancer risk since functional polymorphisms in folate-related genes contribute to the alteration of folate metabolism. Therefore, *MTHFR* polymorphisms have been intensively studied in breast cancer and the results are inconsistent (44;45).

However, a study performed with 456 breast cancer cases and 912 controls observed that breast cancer risk was inversely associated with consumption of dietary folate and none of the polymorphisms (*MTHRF, MTRR, MTR*) showed any significant impact on breast cancer risk. In postmenopausal women was found a significant increased risk of breast cancer among individual with the *MTHFR* 677TT genotype compared with those with the *MTHF*R 677CC genotype. The study showed a significant interaction between the *MTRR* A66G and folate intake. The *MTRR* 66GG genotype increased the risk among postmenopausal women with low intake of folate (46).

Hyperhomocysteinemia and Depression

Folate and vitamin B12 deficiency, HHcy and the 677T allele of the *MTHFR* gene, which cause impaired methylation reactions in the central nervous system, had been associated with depressive disorders (47). However other studies had not found such association (48,49).

A prospective study with 732 Korean subjects investigated associations between folate, vitamin B12, Hcy and late-life depression. The incident depression was predicted by lower folate and vitamin B12 levels and higher Hcy levels performed 2 years previously, and was associated with a decline in vitamin B12 levels and an increased in homocysteine levels over the intervening period. However, incident depression was not associated with *MTHFR* genotype (50).

Hyperhomocysteinemia and Diabetes

Mild Hcy has been observed in type I diabetic patients with microalbuminuria and nephropathy and may explain the increased risk of vascular disease in this high-risk population (51).

A study conducted in Spain analyzed 46 patients with Diabetes Mellitus between 4 and 19 years of age. This study showed that children with strict control of the diabetes type I had

normal tHcy, with no significant difference comparing to healthy individuals of the same age and social environment (52). It was hypothesized that oral administration of folic acid would reduce plasma Hcy levels, improving endothelial function and oxidative stress in patients with type I diabetes and microalbuminuria. A case-study showed a 25% reduction in plasma Hcy after folic acid supplementation in diabetes subjects (53).

Hyperhomocysteinemia and Drugs

There is evidence to support the unfavorable effects of some anti-epileptic drugs on plasma homocysteine concentrations. Approximately 10-40% of epileptic patients develop HHcy (54;). The levels of HHcy were increased in monotherapy using phenytoin, carbamazepine (CBZ) or valproic acid (VPA) (55).

In 2007 a prospective observational study was conducted in Italy to evaluate the influence of antiepileptic drugs and MTHFR polymorphism and levels of Hcy. A higher prevalence of the MTHFR 1298C allele was observed in epileptic patients as compared to the controls. After folate therapy, plasma tHcy and folate were normal in all patients. (56).

Management of Hyperhomocysteinemia

Elevations in plasma homocysteine are common in the general population, particularly in the elderly. Vitamin status is a primary determinant of mild-to-moderate HHcy and accounts for approximately two thirds of all such cases. Vitamin supplementation results in near normalization of plasma homocysteine in most cases Homocysteine metabolism requires the participation of folate as well as vitamin B12 (cobalamin) and vitamin B6 (pyridoxal phosphate) coenzymes and therefore reduction of homocysteine levels in plasma requires that all three of these vitamins are supplemented (1). The minimum daily requirement of folic acid is 50μg, although the current recommended intake is 400μg/day for the average adult and 600μg/day during pregnancy (57).

A large study with 750 male observed that dietary intervention with increased focus and availability of vegetables, fruits and bread, significantly reduced the concentration of tHcy. These findings suggest that the changes in the concentration of cysteine, folate and flavin mononucleotide seem to be predictors of changes in the tHcy concentration (58).

Fortification of grain food with folic acid to decrease the incidence of NTD started in USA and Canada in 1998. This public health strategy lowered the tHcy concentrations leading not only to decrease of the prevalence of congenital anomalies but also decline in the incidence of stroke mortality (59).

Conclusion

In the last decade several studies had been conducted to uncover the direct or indirect influence of increased levels of Hcy in several conditions.

It was demonstrated that several polymorphisms in genes in the homocysteinemethionine pathway result in HHcy, suggesting that these variants may play a role in many multifactorial disorders of high prevalence in the general population.

Vitamin supplementation is a cost effective way to decrease HHcy and the broad vitamin supplementation would prevent at least some of these disorders.

Despite these robust indications about the role of HHcy as a factor associated to several conditions, long-term studies in large samples are still lacking to prove that decreasing the Hcy levels in subjects with HHcy results in better results in terms of health outcomes.

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Figure 1.
Homocysteine metabolism

Table 1

Classification of hyperhomocysteinemia (according to Selhub, 1999)

Severe hyperhomocysteinemia
High total homocysteine (tHcy) levels at all times (31- >100mmol/L), caused for example by deficiencies in Cystathionine beta synthase (CBS), methylenetetrahydrofolate reductase (MTHFR), or in enzymes of B12 metabolism
Mild hyperhomocysteinemia
Moderately high tHcy levels (15-30 mmol/L) under fasting conditions; reflects impaired homocysteine methylation (folate, B12 or moderate enzyme defects, e.g. thermolabile MTHFR)
Post-methionine load
Abnormal increase in tHcy (>15mmol/L) after methionine load (100 mg/kg); reflects impaired homocysteine transsulfuration (heterozygous CBS defects, B6 deficiency)